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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/804,408	03/12/2001	Mathew F. Ogle	1416.20US01	1108

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EXAMINER
NAFF, DAVID M

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 10/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/804,408	OGLE ET AL.	
	Examin r	Art Unit	
	David M. Naff	1651	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 26 September 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☒ The proposed amendment(s) will not be entered because:

(a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☒ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: *See attachment*.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See attachment*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *1-28 and 34-43*.

Claim(s) withdrawn from consideration: _____.

8.☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☒ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). *8/19/02*.

10.☐ Other: _____

David M. Naff
Primary Examiner
Art Unit: 1651

ATTACHMENT TO FORM PTOL-303

The amendment to claim 10 that changes the claim to recite "linkers are substantially nonreactive with respect to unmodified tissue" raises new issues for consideration over prior art and under 35 U.S.C. 112 since this limitation has not been previously claimed and is not disclosed in the specification.

The above noted change in claim 10 raises the issue of new matter since support is not found in the specification for amended claim 10 at page 17, line 25 to page 18, line 10, as asserted by applicants. Page 17, lines 28-29, disclose that "bridges" are generally non-reactive with respect to unmodified tissue. There is no disclosure that "linkers" are non-reactive with unmodified tissue.

In response to the 35 U.S.C. 103 rejection, applicants urge that in Yang et al tissue is already crosslinked with glutaraldehyde to form fixed tissue, and the crosslinked tissue is then reacted with a diamine to replace at least some of the carboxyl groups on the collagen molecules with non-carboxyl side groups without affecting the glutaraldehyde crosslinked portion. However, as shown in Fig 2 of Yang et al, after reacting with a diamine, additional glutaraldehyde is added to form bridges between amino groups of the diamine. In this embodiment of Yang et al, the diamine is the linker and the glutaraldehyde is the bridge molecule. The present invention as broadly claimed does not exclude a diamine being the linker and glutaraldehyde being the bridge molecule. Additionally, the claims do

not exclude the tissue containing crosslinking prior to adding a linker and bridge molecule.

As to claims where the linker can contain an aldehyde group and be glutaraldehyde, as pointed out in the previous office action of 5/20/03, all glutaraldehyde will not contain both ends bound to tissue when crosslinking occurs in Ogle et al and Yang et al, and when the diamine is added there will be some free ends of the glutaraldehyde that will react with the amine groups of the diamine. In an embodiment of the present invention, the present specification discloses (page 24, lines 21-22) that the linker and bridge molecule can be applied to the tissue sequentially. If both ends of glutaraldehyde react with tissue as asserted by applicants, then this embodiment will not work since the tissue is contacted with the glutaraldehyde in the absence of the bridge molecule as in Ogle et al and Yang et al. The fact that this sequential embodiment works supports that some free aldehyde groups will remain after crosslinking tissue with glutaraldehyde as disclosed by Ogle et al and Yang et al. The present claims do not exclude activating carboxyl groups as in Yang et al prior to adding the diamine, and diamine reacting with the activated carboxyl group in addition to free aldehyde groups. The fact that free amine groups remain after reacting activated carboxyl groups with the diamine further supports that free aldehyde groups will remain after reacting with glutaraldehyde to crosslink. The present specification discloses (page 17, lines 11-12) that the tissue can be modified by reacting with activators, and that functional

groups of the bridges react with linkers and modified tissue (page 18, lines 22-25).

Applicants urge that free aldehyde groups will not remain after crosslinking as disclosed by Ogle et al since Ogle et al selected glutaraldehyde oligomers of a size to span the gap between sites to fix the tissue. However, the glutaldehyde oligomers of Ogle et al can contain oligomers of 3 monomers (col 6, line 37) which will be less than 25 Angstroms as disclosed in the present specification. Additionally, the glutaraldehyde oligomer of Ogle et al will contain glutaraldehyde monomer in combination with the oligomer and the monomer will also be within the Angstrom range disclosed in the specification. As is apparent from instant claim 24, treatment with the linker can be as long as one month. This is clearly a longer time than the 6 days used by Ogle et al (col 9, line 6). When treating with a glutaraldehyde linker, the present claims encompass fixing tissue in the same way as Ogle et al.

Applicants urge that claims 34 and 36 require bridge molecules bonded to two or more modified sites of the tissue. However, this encompasses the embodiment shown by Fig 2 of Yang et al where glutaraldehyde bridges free amine groups of diamines reacted with activated carboxyl groups of tissue. The claims do not specify how modification is accomplished, and modified sites could be formed by reacting carboxyl groups of tissue with a diamine as disclosed by Yang et al. As to claims 35 and 37 that require modified sites to comprise aldehyde groups, this would encompass first crosslinking tissue with

glutaraldehyde and then reacting with a diamine as in Yang et al. As noted, free aldehyde groups will remain after crosslinking, and the claims do not exclude activating carboxyl groups before adding the diamine.

In regard to a diamine being a linker and glutaraldehyde being a bridge molecule, applicants urge that glutaraldehyde is a known linker as taught in Ogle et al and Yang et al. However, neither of these references use the term "linker" when referring to glutaraldehyde. While crosslinking may inherently involve linking, reacting with a diamine as disclosed by Yang et al also inherently involves linking. Since the diamine links the tissue to glutaraldehyde, the diamine can also be considered a crosslinker. There is no recognition in the prior art that a linker function requires a crosslinking agent such as glutaraldehyde and that a bridging function requires a diamine. A linker is inherently a bridge molecule and a bridge molecule is inherently a linker.

Applicants urge that there is no teaching in the prior art how to modify glutaraldehyde so that it will not polymerize spontaneously. However, there is no teaching in the present specification how to modify glutaraldehyde so that it will not polymerize spontaneously. The present specification (page 25, line 3) discloses using the screening method of Ogle et al. This screening method produces a glutaraldehyde composition containing glutaraldehyde monomer and oligomers thereof (claim 15 of Ogle et al). There is no description in Ogle et al of how to use the screening method to obtain only

monomers, and the present specification fails to describe how to screen to obtain only glutaraldehyde monomer. Therefore, it appears applicants are using glutaraldehyde monomer and oligomers thereof as used by Ogle et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is 703-308-0520. The examiner can normally be reached on Monday-Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on 703-308-4743. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

David M. Naff
Primary Examiner
Art Unit 1651

DMN
10/24/03